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Inotropic actions of lignocaine and phenytoin

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Summary

1. The inotropic effects of two antiarrhythmic drugs, lignocaine and phenytoin, were studied in electrically driven isolated rabbit atrial preparations. The time-effect relationship of each drug was investigated with different concentrations and frequencies of stimulation.

2. The effects of time of exposure, drug concentration and heart rate on the development of beat alterations (cessation of beat, skipped beat, alternating variation of force of contraction and extrasystole) were also studied.

3. When the chronotropic effects of both drugs were prevented, the inotropic effects were positive or negative depending on the concentration of drug, time of exposure and frequency of stimulation.

4. At concentrations higher than those obtained in the blood of man on maintenance doses, alteration of the beat occurred but was consistent with the peak blood concentrations immediately after the injection of standard clinical doses. The time of onset of beat alteration shortened when either drug concentration or frequency of stimulation was increased.

5. The beat alteration produced by antiarrhythmic drugs can account for various adverse effects associated with their clinical use. These effects include transient ventricular tachycardia and extrasystole during and shortly after injection of drug, ventricular tachycardia, ventricular fibrillation and cardiac arrest due either to excessive dose or to persistent tachyarrhythmia if the dose is not excessive.

Introduction

Lignocaine and phenytoin are effective in abolishing a variety of cardiac arrhythmias in laboratory animals and human patients, and lignocaine is a popular drug in the treatment of ventricular arrhythmias. It is most effective in abolishing ectopic activity associated with acute myocardial infarction (Lown & Vassaux, 1968). However, its use as a prophylactic drug has been challenged by reports of serious adverse effects including ventricular tachycardia and fibrillation (Kaufman, 1968; Nagle & Pilcher, 1968). Furthermore, a large percentage of patients died as the result of these adverse effects (Chopra, Portal & Aber, 1969). These indicate a need for more work on lignocaine.

Most haemodynamic studies using clinically effective antiarrhythmic doses have

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not revealed important undesirable effects on the cardiovascular functions of patients with coronary infarction (Jewitt, Kishon & Thomas, 1968; Stannard, Sloman & Sangster, 1968), but a tendency to depress myocardial contractility existed in all these studies, especially with higher doses. Depression of myocardial contraction has been reported in anaesthetized dogs (Austen & Moran, 1965) and isolated rabbit atria (Covino & Shannon, 1969).

Phenytoin was proposed as an antiarrhythmic agent at about the same time as lignocaine but its acceptance as a useful antiarrhythmic drug has been slow. Although the drug has some unique effects on the electrophysiological properties of the heart (Bigger, Schmidt & Kutt, 1968) it also produces myocardial depression (Mierzwiak, Mitchell & Shapiro, 1967; Nayler, McInnes, Swann, Race, Carson & Lowe, 1968) in doses required for therapeutic action (Covino & Shannon, 1969). Several deaths from cardiac arrest and fibrillation have been reported following the use of phenytoin (Mercer & Osborne, 1967; Gellerman & Martinez, 1967; Goldschlager & Karliner, 1967).

This report deals with the effects of lignocaine and phenytoin on the contractility of isolated rabbit atria at various frequencies of electrical stimulation, the progress of such effects with time, and their relation to the concentration of drugs. The importance of these parameters in the production of abnormal beating patterns was also included.

Heart rate can have a profound influence on myocardial contractility and the action of drugs on contractility. A drug with both chronotropic and inotropic actions can change the force of contraction both directly and indirectly through its effect on heart rate. These two effects may oppose or add to each other depending on the location and the frequency–strength curve of the heart rate under study. The heart rate also influences the rate of onset of drug action (Kock-Weser & Blinks, 1963).

These phenomena are important in understanding the therapeutic and toxic effects of antiarrhythmic drugs. Thus, quinidine decreases heart rate in spontaneously beating atria of rats and guinea-pigs, but increases the force of contraction in the rat and decreases it in the guinea-pig. When the decrease in heart rate due to quinidine is prevented by electrical stimulation a positive inotropic effect is seen in both atria (Kruta, 1963). In clinical tachyarrhythmias, the depression of contractility would be compensated by the improvement of cardiac function due to reduction in the rate in response to quinidine; if the arrhythmia failed to respond, quinidine would not be expected to produce adverse effects by further depression of myocardial contractility. Whether this type of argument applies depends on the existing heart rate and the knowledge of drug actions in terms of the concentration of drug and frequency-force relationship of the myocardium.

With the exception of those on quinidine, no report has appeared in which the effects of other antiarrhythmic drugs on contractility was studied in relation to the frequency-force relationship of the heart. The data from this study will be compared with those for quinidine so that the importance of inotropic actions of the antiarrhythmic drugs in therapy can be assessed.

Methods

Experiments were carried out on atria isolated from rabbits of either sex weighing 2–3 kg. The left atria and the right atria, with pace-makers removed, were used

separately and the data from both atria combined. No apparent and statistically significant differences were observed between the two atria. Each atrial preparation was used for only one drug at one concentration and one frequency of stimulation. The preparations were mounted in tissue baths (15 ml maximum volume) containing a bathing solution of the following composition (mmol/l.): Na, 157·3 ; K, 5·4 ; Ca, 2·2 ; Cl, 153·0 ; HCO_3, 11·9 ; glucose, 11·0 ; pH 7·4 (Kennedy & West, 1969). The temperature of the bath was maintained at 35° C. The bath was bubbled with 95% oxygen and 5% carbon dioxide.

The bases of the atria were attached to two stainless steel electrodes. Electrical stimulation was by rectangular pulses of 5 ms duration at 1·3 times threshold voltage. All preparations were stimulated at the frequency of 1 Hz for 60 min before the experiment was performed. At that time, the frequency of stimulation was changed to the desired one. Drugs were added 30 min after switching to the desired frequency.

The force of isometric contraction was measured by a force displacement transducer with an appropriate preamplifier and recorded on chart paper. Changes in force of contraction were reported in terms of percentage increase or decrease relative to the control values recorded before adding the drug to the bath.

Drug solutions were prepared so that a constant volume of 0·1 ml of the solutions was added to 10 ml of bathing fluid. All concentrations are in terms of the salt.

All chemicals used were A.R. quality. Double glass-distilled water was used for making solutions. Xylocaine hydrochloride monohydrate (Astra Pharmaceutical Products, Inc., Worcester, Mass., USA) was dissolved in distilled water. The sodium salt of phenytoin (Mann Research Laboratories, New York, NY, USA) was dissolved in 0·01 N NaOH.

Statistical significance of difference was determined by Student's *t* test taking a probability of 5% as significant.

Results

Table 1 summarizes the changes in the force of isometric contraction of the isolated atria over 120 min in the tissue bath containing lignocaine. Each entry is the mean ± S.E. of five atria. The means for each frequency of stimulation are plotted against time after addition of drug in Fig. 1 (A, B, C, and D).

The data from the control experiments in which 0·1 ml of distilled water was added instead of drug indicate that there was spontaneous decline in the force of contraction at all four frequencies of stimulation studied. This spontaneous decline was slowest when the frequency of stimulation was 2 Hz. At the end of the 120 min the force of contraction was only slightly lower than at 0 minutes. Frequencies of stimulation higher or lower than 2 Hz resulted in much more reduction in force at the end of the experiment, more rapid onset of spontaneous decline and faster rate of decline.

Changes in the force of isometric contraction produced by lignocaine

At the stimulation frequency of 0·1 Hz, lignocaine caused almost immediate reduction in the force of contraction. The control atria did not exhibit a significant reduction in force until after 30 min, but in the presence of lignocaine at concentra-

tions of 1, 3, 5 and 10 μg/ml, the force of contraction decreased rapidly as soon as the drug was introduced. This initial decline was more rapid than the spontaneous decline in the control occurring after 30 minutes. However, it stopped within 20 min ; thereafter, the rate of decline was parallel with the decline in the control.

The patterns of response at other stimulation frequencies were qualitatively similar to those described for the frequency of 0·1 Hz. Except at the lowest con-

TABLE 1. *Changes in isometric force of contraction of isolated rabbit atria after addition of lignocaine*

Drug conc. (μg/ml)	Beats/s	% Change from control (mean ± S.E.): time after drug (min) 5	10	15	30	45	60	80	100	120
0	4	− 1·5 ± 1·0	− 3·3 ± 1·6	− 5·3 ± 3·1	− 5·1 ± 4·1	− 6·9 ± 4·8	− 7·5 ± 4·5	−11·0 ± 4·6	−15·1 ± 5·3	−18·7 ± 5·9
	2	− 1·3 ± 0·8	− 1·3 ± 0·8	− 0·8 ± 0·8	+ 0·9 ± 2·4	+ 1·0 ± 1·3	+ 0·2 ± 2·2	− 2·1 ± 3·0	− 4·2 ± 2·5	− 6·0 ± 3·6
	1	0·0	− 1·3 ± 0·8	− 1·3 ± 0·8	− 4·5 ± 1·5	− 6·1 ± 2·1	− 8·8 ± 3·0	−11·3 ± 3·9	−15·5 ± 3·2	−15·9 ± 5·3
	0·1	0·0	0·0	0·0	− 1·7 ± 3·2	− 5·1 ± 3·0	− 6·8 ± 4·6	−11·5 ± 2·6	−14·0 ± 3·7	−17·0 ± 2·5
1	4	− 4·2 ± 1·1	− 9·8 ± 3·1	−10·0 ± 2·4	−13·8 ± 4·0	−14·2 ± 4·8	−18·5 ± 7·7	−22·4 ± 8·3	−26·3 ± 8·3	−29·4 ± 9·0
	2	− 0·8 ± 0·7	+ 0·6 ± 0·3	+ 0·1 ± 0·6	+ 3·5 ± 0·7	+ 3·3 ± 1·0	+ 3·2 ± 1·1	+ 2·7 ± 1·0	+ 1·7 ± 1·1	+ 1·8 ± 1·1
	1	− 5·3 ± 4·0	− 4·1 ± 2·4	− 4·7 ± 2·4	− 3·0 ± 2·2	− 1·5 ± 3·4	− 4·2 ± 2·7	− 8·4 ± 3·5	−12·1 ± 4·0	−17.4 ± 4·1
	0·1	− 4·2 ± 1·9	− 6·6 ± 2·5	−10·1 ± 3·9	−13·0 ± 4·9	−15·6 ± 6·9	−17·5 ± 9·0	−17·5 ±12·6	−20·3 ±12·8	−23·2 ±14·5
3	4	− 7·0 ± 1·9	− 7·2 ± 2·4	− 9·3 ± 2·0	−11·9 ± 2·8	−11·1 ± 2·7	−13·2 ± 3·5	−13·6 ± 2·2	−16·8 ± 3·4	−17·3 ± 3·7
	2	− 4·6 ± 1·0	− 4·9 ± 1·1	− 4·2 ± 1·6	− 3·6 ± 2·1	− 5·3 ± 1·7	− 6·1 ± 1·8	− 7·5 ± 1·9	− 9·2 ± 1·9	−12·6 ± 2·2
	1	−13·5 ± 2·8	−15·5 ± 4·9	−17·6 ± 6·3	−17·9 ± 9·6	−18·6 ± 9·9	−23·3 ±10·9	−27·3 ±10·0	−31·7 ± 9·8	−37·0 ± 9·2
	0·1	− 4·4 ± 1·4	−12·2 ± 2·7	−14·9 ± 3·8	−17·9 ± 4·7	−21·0 ± 4·7	−24·9 ± 5·2	−28·2 ± 6·3	−32·8 ± 5·7	−35·8 ± 5·6
5	4	− 9·3 ± 3·6	−10·7 ± 2·2	−17·2 ± 2·4	—	—	—	—	—	—
	2	−13·5 ± 1·6	−17·0 ± 3·6	−16·6 ± 4·6	−13·5 ± 7·5	−12·7 ± 9·5	− 8·8 ± 0·2	−10·7 ± 1·2	−11·3 ± 4·2	−15·7 ± 7·1
	1	−10·4 ± 1·8	−16·8 ± 4·2	−17·0 ± 4·6	−11·7 ± 6·1	−14·4 ± 5·8	−13·6 ± 7·4	−14·2 ± 8·8	−15·7 ± 9·5	−14·8 ±10·7
	0·1	− 7·1 ± 1·4	−16·5 ± 7·1	−20·2 ± 5·6	−19·5 ± 6·3	−21·9 ± 7·3	−24·5 ± 8·5	−28·3 ± 9·1	−29·3 ±10·8	−33·3 ±10·5
10	2	−23·8 ± 0·5	−27·6 ± 1·1	−27·6 ± 1·1	−28·0 ± 1·5	−29·1 ± 1·4	−29·4 ± 3·0	−30·9 ± 3·0	−40·3 ± 2·9	−36·6 ± 2·8
	1	−11·7 ± 3·2	−15·0 ± 3·3	−15·0 ± 2·6	−15·4 ± 3·0	−16·8 ± 3·8	−18·3 ± 4·4	−21·8 ± 5·9	−30·0 ± 6·1	−30·5 ± 6·0
	0·1	− 9·4 ± 2·7	−19·9 ± 1·5	−24·3 ± 0·8	−37·0 ± 1·7	−36·8 ± 2·2	−41·4 ± 4·4	−43·0 ± 3·5	−48·1 ± 4·0	−52·6 ±11·1

centration studied (1 μg/ml), lignocaine produced an initial rapid decrease in force of contraction followed, in a short time, by a slower rate of decline of the same magnitude as that of the controls for each frequency of stimulation.

This pattern was particularly obvious when the stimulation frequency was 2 Hz. At this frequency, the rate and magnitude of decline in contractile force of the control throughout the entire period of measurement was relatively small. The rate of decline after the initial phase in the presence of lignocaine was also small. The lowest concentration of 1 μg/ml produced no reduction in force during the initial phase followed by a slight increase which, at the end of the experiment, remained higher than the force of contraction before lignocaine was added. With the concentration range of lignocaine studied, effects do not always increase with increasing concentrations of drug. Statistical analysis indicated that the effects due to 10 μg/ml lignocaine were significantly different from the changes which occurred in the absence of drug at comparable times throughout the entire period of measurement. However, this does not apply when comparisons were made between the effects due to one concentration with effects due to others or with the control.

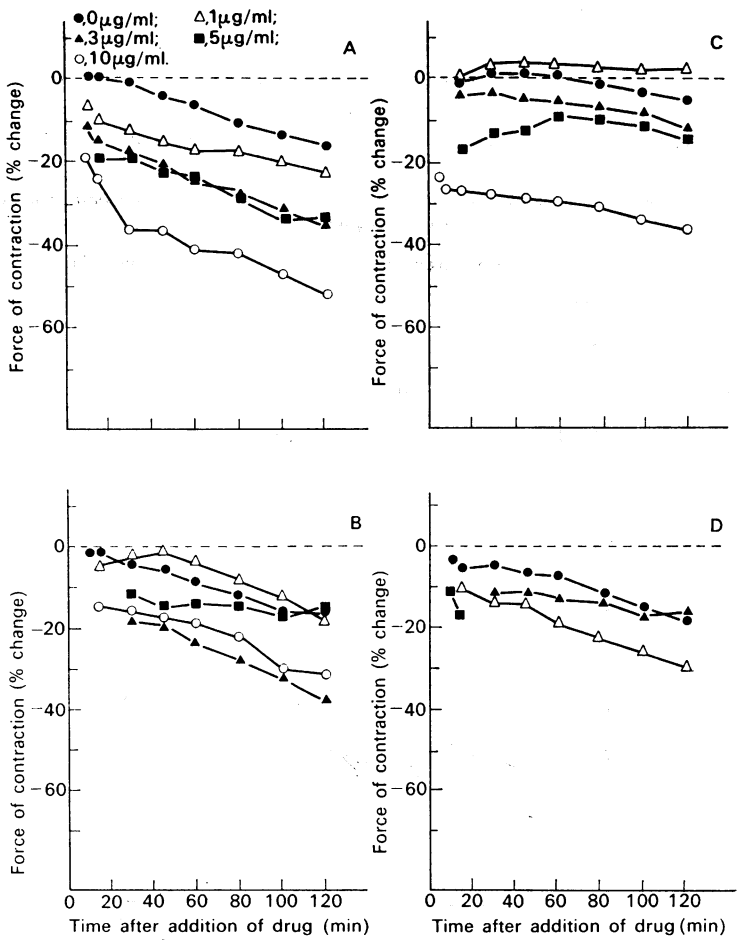

FIG. 1. Changes in the force of isometric contraction after administration of lignocaine to electrically driven isolated rabbit atrial preparations. Each point represents the mean of five atria. The atria were driven at frequencies of (A) 0·1 Hz; (B) 1 Hz; (C) 2 Hz; (D) 4 Hz. The concentrations of lignocaine in the bath are given in the key.

The percentage reductions in the force of contraction 10 min after addition of lignocaine to the bath were plotted against the logarithms of concentration (Fig. 2). The dose-response curves are different at different heart rates.

From these data, it can be concluded that lignocaine has intrinsic negative inotropic action unrelated to changes in heart rate. This negative inotropic action reaches its maximum 10–20 min after exposure and does not increase further on continued exposure to the drug; but the maximum negative inotropic effect is maintained as long as the drug is present. At a concentration comparable to the peak blood concentration after single intravenous injection of the therapeutic dose in man (10 μg/ml according to Jewitt *et al.* (1968)), the force of contraction of isolated rabbit atrium is reduced by 15–35%. At effective antiarrhythmic blood concentrations (1·5–2·5 μg/ml) the reduction was around 10%.

Alterations of heart beat produced by lignocaine

In the experiment reported above, alteration of heart beat occurred only at the frequency of stimulation of 4 Hz and only when the concentration of lignocaine in the bath was 5 μg/ml or higher. The alteration appeared as one of the following: sudden cessation of beat; skipped beat; alternating variations in the amplitude of contraction; or extrasystole. All types could be temporarily reversed by raising the stimulus intensity but returned after a few minutes. The time of onset of altera-

TABLE 2. *Time of onset of alteration in the beat due to lignocaine in isolated rabbit atria stimulated at various frequencies*

Drug conc. (μg/ml)	Time of onset (min) (mean ± S.E.): frequency (Hz)				
	5 Hz	3 Hz	2 Hz	1 Hz	0·1 Hz
5	25·0±7·3	—	—	—	—
10	2·4±0·4	4·8±1·0	—	—	—
50	0·5±0·3	—	4·0±1·1	9·3±1·8	6·9±1·8
100	0·6±0·2	—	2·4±0·7	6·8±1·6	4·6±1·3

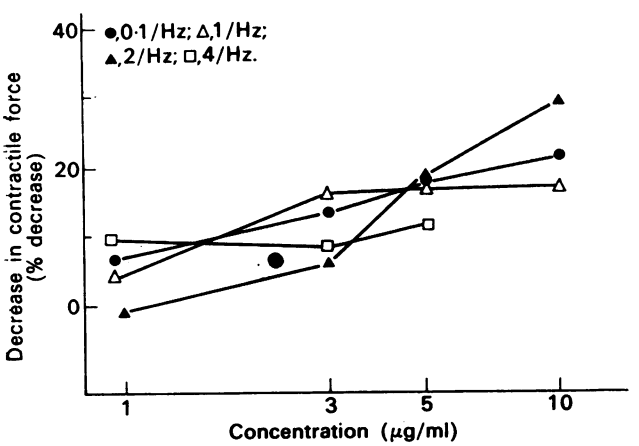

FIG. 2. Percentage decrease in isometric force of contraction 10 min after the administration of lignocaine. The abscissa represents the concentration of drug in the bathing fluid. The frequencies of stimulation are given in the key.

tions in heart beat was studied in a new set of atrial preparations using higher concentrations of lignocaine. The results are summarized in Table 2 and Fig. 3. The time interval from the administration of lignocaine to the first appearance of the altered beat was recorded as the time of onset. If no alteration occurred in 2–3 h, it was assumed that none would occur. The lower concentrations of 5 and 10 μg/ml lignocaine produced alteration in the beat only at the higher frequencies of stimulation, while higher concentrations of 50 and 100 μg/ml produced alteration in the beat at all frequencies of stimulation studied. The alteration in beat due to the two higher concentrations of lignocaine occurred rapidly at all frequencies of stimulation. No statistically significant difference was observed between the two concentrations although both were significantly shorter than the times of onset due to the two lower concentrations. For each concentration of lignocaine producing altered beats at more than one frequency of stimulation there are statistically significant differences between the times of onset for each frequency except between frequencies of 1 Hz and 0·1 Hz.

Both negative inotropic effect and alteration of beat could be reversed by washing the drug out of the bath. Recovery occurred rapidly within 5–10 minutes.

Changes in the force of isometric contraction produced by phenytoin

The same experimental design used in studying lignocaine was applied to phenytoin. The results are summarized in Table 3 and Fig. 4 (A, B, C, and D).

Because the solvent for phenytoin was 0·01 N NaOH, a new set of control data was obtained for the effects of the solvent. The pH of 10 ml of the bathing media remained at 7·4 after 0·1 ml of the NaOH solution was added. No apparent quali-

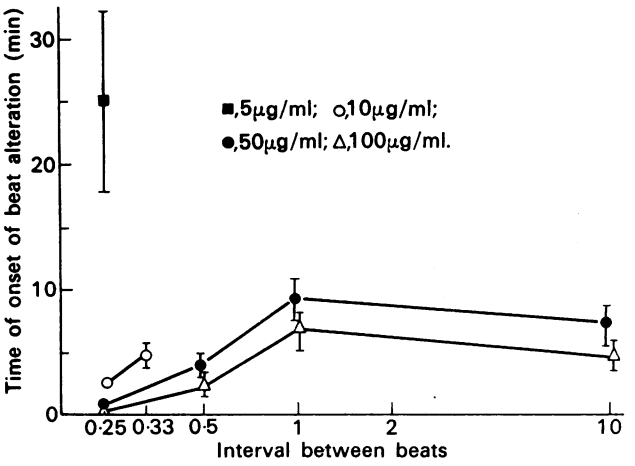

FIG. 3. Effects of frequency of electrical stimulation and concentration of lignocaine on the time of onset of beat alteration. The mean times of onset and S.E.M. are given when the concentrations of lignocaine in the bath were as in the key.

TABLE 3. *Changes in isometric force of contraction of isolated rabbit atria after addition of phenytoin*

Drug conc. (μg/ml)	Beats/s	% Change from control (mean ± S.E.): Time after drug (min) 5	10	15	30	45	60	90	120
0	2	1·0 ± 1·0	− 1·1 ± 3·2	− 0·1 ± 4·2	− 0·1 ± 4·2	2·1 ± 2·1	2·1 ± 2·1	0·9 ± 5·2	1·9 ± 8·4
	1	− 1·1 ± 1·1	− 1·1 ± 1·1	0·0 ± 0·0	− 0·2 ± 1·9	± 1·9 ± 0·2	− 3·0 ± 1·3	− 8·1 ± 2·9	−11·8 ± 1·4
	0·5	3·1 ± 3·1	0·0 ± 0·0	3·1 ± 3·1	6·2 ± 6·2	− 3·7 ±16·2	− 0·6 ±19·3	− 1·0 ±10·0	−16·2 ± 3·7
	0·1	− 1·0 ± 1·0	− 1·0 ± 1·0	− 1·0 ± 1·0	− 1·0 ± 1·0	− 1·9 ± 1·9	− 6·5 ± 3·6	−12·7 ±12·7	−12·7 ±12·7
0·1	2	0·0 ± 0·0	3·2 ± 3·2	3·2 ± 3·3	3·3 ± 2·3	− 1·4 ± 3·9	− 0·1 ± 4·7	− 8·9 ±11·4	−11·9 ±12·0
	1	0·5 ± 0·5	4·8 ± 1·2	5·7 ± 2·6	9·3 ± 5·1	8·5 ± 5·6	8·2 ± 7·5	3·6 ± 5·7	− 7·2 ± 7·1
	0·5	3·1 ± 4·8	6·2 ± 5·3	5·8 ± 4·5	10·9 ± 7·1	18·5 ±11·5	22·5 ±12·9	25·2 ±13·8	24·1 ±13·7
	0·1	1·5 ± 3·3	1·5 ± 3·3	0·3 ± 4·1	3·5 ± 5·4	− 3·0 ± 8·7	− 0·9 ±15·3	−10·8 ±11·6	−23·1 ±13·4
1	2	0·4 ± 0·4	1·2 ± 1·8	2·8 ± 2·0	4·7 ± 3·8	6·5 ± 4·6	3·8 ± 5·6	0·7 ± 4·0	1·7 ± 2·7
	1	− 1·1 ± 1·1	0·0 ± 0·0	2·3 ± 2·3	3·5 ± 1·5	4·8 ± 2·2	4·4 ± 2·9	− 1·7 ± 3·7	− 7·3 ± 2·4
	0·5	0·0 ± 0·0	2·2 ± 1·2	5·2 ± 3·0	1·6 ± 1·0	3·5 ± 5·1	− 5·5 ± 4·7	−13·3 ± 5·5	−21·0 ± 6·6
	0·1	− 0·7 ± 2·3	0·1 ± 3·9	− 2·2 ± 5·8	− 5·2 ± 7·6	−11·6 ± 6·7	−16·7 ± 9·7	−25·2 ±14·0	−35·1 ±12·8
10	2	−13·8 ± 1·9	−15·3 ± 2·9	−17·7 ± 2·9	−20·0 ± 4·2	−20·7 ± 3·6	−24·3 ± 6·3	−26·1 ± 8·0	−30·1 ±11·3
	1	− 9·5 ± 1·1	−16·5 ± 1·4	−23·4 ± 0·8	−28·9 ± 3·0	−37·2 ± 0·6	−40·5 ± 1·9	−47·4 ± 3·0	−53·4 ± 3·4
	0·5	−11·1 ± 2·5	−20·3 ± 4·1	−25·6 ± 5·7	−34·6 ± 6·8	−39·5 ± 9·1	−44·9 ± 6·9	−5·50 ± 7·5	−66·9 ± 7·6
	0·1	−17·9 ± 7·0	−25·3 ± 7·6	−20·4 ±10·3	−37·2 ± 8·0	−41·5 ± 8·7	−46·0 ± 6·7	−50·5 ± 5·3	−58·1 ± 5·9
50	2	−33·0 ± 5·5	−50·6 ± 2·7	−55·6 ± 3·5	−63·7 ±12·4				
	1	−38·1 ± 6·1	−56·0 ± 9·9	−65·3 ± 8·5	−72·9 ± 9·8	−77·5 ± 7·5	−87·5 ± 0·0	−90·0 ± 0·0	
	0·5	−53·2 ± 1·2	−77·0 ± 7·6	−91·6 ± 0·0					
	0·1	−26·2 ±14·4	−40·6 ±15·6	−41·0 ±16·0					
100	2	−68·3 ± 3·4							
	1	−55·1 ± 3·1	−69·9 ±13·3	−88·5 ± 1·3					
	0·5	−44·9 ± 3·9	−68·7 ± 4·2	−65·2 ±10·9					
	0·1	−36·1 ±13·9	−56·9 ±18·0	−50·0 ± 0·0	−77·7 ± 0·0				

tative or quantitative difference between the effects of the solvent for lignocaine and the solvent for phenytoin was detected at any frequency of stimulation.

The importance of heart rate and drug concentration on the inotropic effects of phenytoin was clearly demonstrated by the frequency and concentration ranges used in this study.

At the low frequency of 0·1 Hz (Fig. 4A), the predominant effect was a reduction in the force of contraction. A few preparations showed a slight positive inotropic response during the first 60 min of exposure at the lowest concentration used (0·1 μg/ml) followed by a decline in the force of contraction not readily distinguishable from the spontaneous changes in the control preparations. At 1 μg/ml, only slight variations occurred during the first 20 min of exposure; thereafter the contractile force decreased at a constant rate which was more rapid than that of the control. At the concentration of 10 μg/ml, an immediate rapid decrease in force was observed, followed after 30 min by a slower rate comparable to that seen with

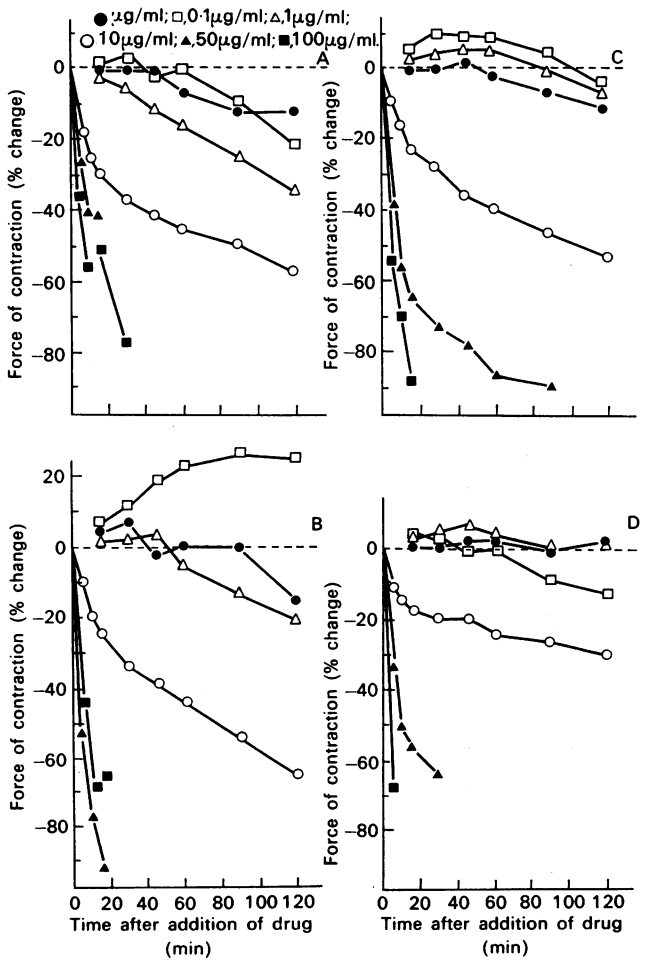

FIG. 4. Time course of change in the force of isometric contraction after administration of phenytoin to electrically driven isolated rabbit atria. Frequencies of stimulation were: (A) 0·1 Hz; (B) 0·5 Hz; (C) 1 Hz; (D) 2 Hz. Each point represents the mean response of five atria. The concentrations of phenytoin in the bath were as shown in the key.

1 μg/ml. The initial rate of decrease in the force of contraction became higher when the concentration of phenytoin was increased to 50 and 100 μg/ml. At these higher concentrations alteration of beat commenced within 20–30 min of exposure to the drug. At a frequency of 0·5 Hz, the above effects were produced by phenytoin at concentrations higher than 1 μg/ml. The small positive inotropic effect due to phenytoin (0·1 μg/ml) seen at the low frequency now became much more obvious. The increases in force of contraction occurring soon after exposure to the drug reached a plateau in about 70 minutes. At frequencies of stimulation of 1 and 2 Hz, the higher concentrations acted as described above. The two lower concentrations showed a tendency to cause a slight increase in the force of contraction.

The changes in the force of contraction 10 min after the addition of the drug were arbitrarily chosen for plotting the dose-response relationship shown in Fig. 5. It can be seen that the relationship was not modified by heart rate.

Alteration of beat produced by phenytoin

Phenytoin (50–100 μg/ml) produced the same kind of alterations in the beat as lignocaine (Fig. 6). The times of onset of beat alteration for each concentration at different frequencies were not significantly different from one another ($P>0·05$); but there was a tendency for onset to occur more quickly at higher concentrations of drug and at higher frequencies of stimulation.

Discussion

The time-effect relationships of lignocaine and phenytoin were determined in conjunction with varying drug concentrations and frequencies of stimulation. These data form a basis for further studies on the mechanism of inotropic effects of antiarrhythmic drugs and for a better understanding of the use of these drugs in clinical situations. The interaction between heart rate and myocardial contractility has been emphasized repeatedly as an important factor in interpreting the inotropic effects of drugs (Koch-Weser & Blinks, 1963; Kruta, 1963); but this has been generally ignored. Thus, despite the repeated demonstrations of the positive inotropic actions of quinidine at certain combinations of concentration and heart rate when the negative chronotropic action is controlled (Kruta *et al.*, 1963; Pruett & Woods, 1967; Kennedy & West, 1969), the drug continues to be considered a depressant of myocardial contractility (Goodman & Gilman, 1970).

We have shown here that lignocaine or phenytoin can increase or decrease myocardial contractility, depending on the heart rate, the concentration of the drug and the duration of exposure to it. The magnitude and the time course of the inotropic effects of the two drugs differ quantitatively, but they are qualitatively similar. Comparing these effects with those of quinidine (Kennedy & West, 1969), it is apparent that all these drugs produce similar effects on myocardial contractility in the isolated rabbit atrial preparations. They produce a positive inotropic action at low concentrations and as the concentration is increased the inotropic action becomes negative. The magnitude and time course of the effect at each concentration are modified by the heart rate. In the isolated, spontaneously beating heart tissue at least, if not in all types of spontaneously beating heart, the effect will be the algebraic sum of that due to change in heart rate and that due to direct action of the drug, independent of heart rate. This is predictable from the frequency and force curve

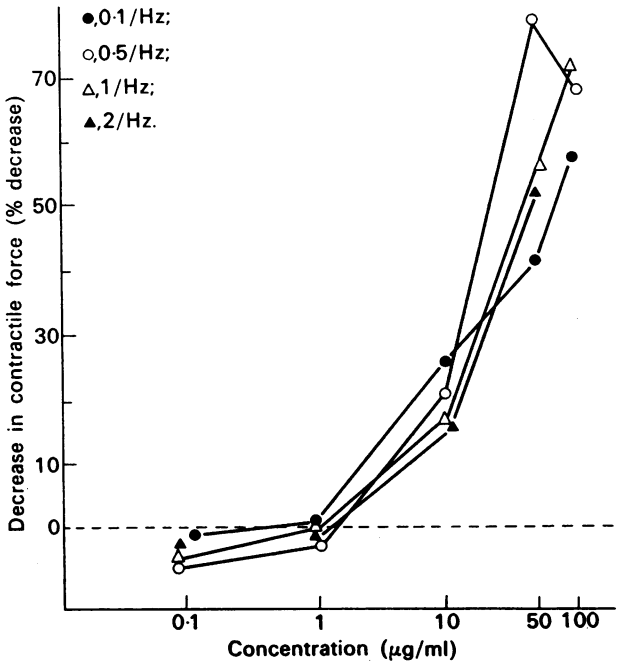

FIG. 5. Percentage decrease in isometric force of contraction after exposure for 10 min to phenytoin at various concentrations as indicated on the abscissa. The frequencies of electrical stimulation were as shown in the key.

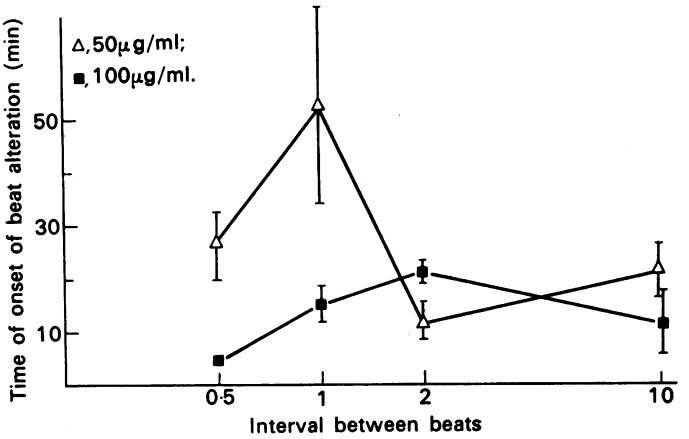

FIG. 6. Effects of stimulation frequency and phenytoin concentration on the time of onset of beat alteration. The mean and S.E.M. are given for the time of onset as shown.

as affected by drug. However, the time dependent characteristic of inotropic effects observed in this study indicates that the determination of such a curve is not always a simple matter. For lignocaine, which results in a steady state after the initial phase of rapid change, the determination of the curve at the steady state is relatively simple. For phenytoin and quinidine in which the action of the drug does not seem to reach equilibrium after long exposure to the drug, the attempt to establish such a curve is confronted with some technical problems. Hence, in considering the effects of antiarrhythmic drugs on myocardial contractility, not only the chronotropic effect has to be taken into account but also the concentration of drug and the duration of exposure to it. With these factors in mind, some problems associated with the therapeutic use of the antiarrhythmic drugs will now be discussed.

The importance of the inotropic effect of antiarrhythmic drugs in therapy is not clear. It has been assumed that even a slight degree of myocardial depression is significant in damaged hearts (Goodman & Gilman, 1970). But to our knowledge, no significant harmful effect of the antiarrhythmic drugs has been linked to their inotropic actions.

When a standard dose of the antiarrhythmic drug is given intravenously for therapeutic purposes, a peak blood concentration is attained at the completion of injection. After the arrhythmia reverts to normal, a blood concentration lower than the peak level is maintained for some time to prevent recurrence. The maintenance blood concentrations are: 5–8 μg/ml for quinidine (Lyon & DeGraff, 1965); 1·5–2·5 μg/ml for lignocaine (Jewitt *et al.*, 1968) and 10–18 μg/ml for phenytoin (Bigger *et al.*, 1968). Similar concentrations of these drugs produce positive or slightly negative inotropic effects in isolated rabbit atria at controlled constant heart rates, including the range of clinical tachycardia and extreme bradycardia. Binding to plasma protein, which can be as high as 60% in the case of quinidine (Conn & Luchi, 1961), further reduces the likelihood of overt depression of myocardial contractility. Therefore, adverse effects in man are probably not related to myocardial depression if data from our rabbit atrial preparations are applicable to human ventricles.

In this study, both lignocaine and phenytoin produced alteration in the beat when the concentration of drug exceeded a certain level. The time of onset of alteration of the beat was reduced by a high concentration of drug or high frequency of stimulation. The same characteristic was reported for quinidine (Kennedy & West, 1969). Clinically, cardiac arrest not related to atrioventricular blockade, ventricular tachycardia and fibrillation have been observed with the antiarrhythmic drugs. The risk of these life-threatening arrhythmias increases with the dose used, but often occurs at doses not considered to be excessive (Selzer & Wray, 1964). Ventricular tachycardia and fibrillation may occur after single injection of lignocaine in arrhythmias which fail to respond to the drug (Chopra *et al.*, 1969) or after further injections when the first injection caused neither harm nor good (Kaufmann, 1968; Nagle & Pilcher, 1968). The latter authors also found that a transient increase in the number of ventricular extrasystoles often occurs while the injection is being given in patients who respond well to the drug. The increase in the number of extrasystoles remains for a further 2–3 min after the end of injection before cessation of ectopic beats. Unger & Sklaroff (1967) reported two deaths from cardiac arrest during an attempt to terminate atrial flutter with phenytoin. Atrial flutter practically never responds to phenytoin (Mercer & Osborne, 1967).

It is likely that the beat alterations observed in our preparations are the basis of the toxic effects in human. The beat alteration is probably equivalent to the ventricular arrhythmias observed in the patients. The concentration of drug producing alteration in the beat is comparable to the peak blood concentration. The clinical observations summarized above can be explained in terms of the factors influencing the appearance of beat alteration. The sensitivity of a particular heart, the magnitude of the peak blood level, the duration at which the level capable of producing beat alteration is maintained and the existing heart rate with associated changes due to the action of drug are important determinations of arrhythmias produced by antiarrhythmic drugs. These considerations emphasize the necessity of slow injection. It is interesting that great success in the use of lignocaine was achieved by slow injection (Jewitt *et al.*, 1968) in contrast to a large proportion of deaths by rapid injection (Chopra *et al.*, 1969). It is also obvious that the antiarrhythmic drugs should not be used in tachyarrhythmias which do not respond to the drug.

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